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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/790,658
Filing Date: March 01, 2004
Appellant(s): BLUME ET AL.

Margaret Sampson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3-20-06 appealing from the Office action mailed 5-17-05.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

Appellants' statement identifying the related appeals, which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal on the following pending applications is correct:

1. Serial No. 10/885,221, Anthony R. DiSanto, filed July 6, 2004.

2. Serial No. 10/806,494, Mark G. Resnick, filed March 3, 2004.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after rejection of claims dated 5-17-05 has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Barton et al. "Neurological complications of Kaposi's sarcoma: An analysis of 5 cases and a review of literature". J. Neurooncol. vol 1, no. 4 (1983), pp. 333-346.

Balsa et al. "Monoamine oxidase activities in lymphocytes and granulocytes taken from pig blood". Biochem. Pharmacol. vol 36, no. 1 (September 1,1987), pp. 2723-2728.

Borbe et al. "Kinetic evaluation of MAO-B activity following oral administration of Selegiline and Desmethyl-selegiline in the Rat". J. Neural. Transm. vol. 32 (1990), pp. 131-137.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

Claims 26 and 34-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Examiner notes that the office actions dated 10-21-04 and 5-17-05, included claims 26, 34 and 38-62 in the first line of the rejection, whereas the limitations of claims 35-37 have also been addressed in the body of the rejection, along with the limitations of claims 26, 34 and 38-62. Accordingly, the rejection under this section is applicable to claims 26 and 34-62.

Instant claims recite a method of treating "a condition" produced by immune system dysfunction that is associated with reduced levels of gamma-interferon production, comprising administering R(-) desmethylselegiline (DMS), wherein the administration leads to an increased production of gamma-interferon in the mammal. Instant claims are broad as they encompass a number of "conditions" that are stimulated or caused by immune dysfunction or immune deficiency.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: nature of the invention, breadth of the claims, state of the art, guidance of the specification, predictability if the art, and the working examples. All the factors have been considered with regard to the claim, with the most relevant factors discussed below.

Nature of the Invention: All rejected claims are drawn to a method of treating "a condition" produced by immune system dysfunction that is associated with reduced levels of gamma-interferon production, comprising administering R(-) desmethylselegiline (DMS), wherein the administration leads to an increased production of gamma-interferon in the mammal. The nature of the invention is extremely complex in that it encompasses anticipating multiple complex diseases or disorders and subsequently administering the instant composition. The breadth of the claims exacerbates the complex nature of the claims. The claim encompasses treating complex disorders that may have potential causes other than those disclosed in the specification. The term immune dysfunction is not necessarily manifested by one condition i.e., pathogenesis, disease or disorder. For instance, AIDS (also described in

the instant invention) is a complex of diseases and conditions, which are not necessarily treatable.

State of the Art: The state of the art does not recognize the administration of compositions to treat disorders such as substance abuse, neurological conditions associated with increased monoamine oxidase, reduced dopamine uptake etc. The state of the art also recognizes treating specific infections or diseases by administering gamma -interferon or other immunomodulating interleukins or chemokines. However, the functioning of immune system in response to an infection or a disease or disorder is modulated by not one immunomodualtor molecule but is a complex interplay of several interleukins or chemokines. Further, a reduction in gamma-interferon does not necessarily result in immune system dysfunction. This is particularly evident from the cited references (Immunology, 1996 and Shi et al, J. Immunology 2004) in the case of AIDS, which applicants claims as a condition caused by immune dysfunction and is associated with reduced gamma-interferon. Thus, the described or claimed conditions may or may not be caused by gamma-interferon reduction leading to immune dysfuntion.

Guidance of the Specification: The guidance given by the specification on how to treat the disorders is absent. Instant specification describes the effect of age on T cell function in terms of the levels of IL-2 and IFN-gamma. Further, the specification also describes the effect of DMS in restoring the levels of IL-2 and gamma-interferon. However, instant specification provides no guidance with respect to the procedure of

administering instant composition to mammals for treating any or all of the disorders claimed. Instant specification also fails to provide any guidance or rationale showing that the claimed method is effective in completely treating any or all disorders produced by immune dysfunction, associated with reduced levels of gamma-IFN or to extrapolate the data provided to al immune dysfunction conditions, that are known to-date or yet to discovered.

Predictability of the Art & The Amount of Experimentation Necessary: The specification lacks guidance from the with regard to treating the claimed conditions, such that a completely effective treatment is ensured. Further, the state of the art recognizes that gamma-IFN levels need not necessarily be reduced in all immune dysfunction conditions or disorders. Thus, the lack of guidance from the specification together with unpredictability of reduced IFN levels in all immune dysfunctions (see above references), leads to further unpredictability of the efficacy of DMS in treating conditions produced by immune system dysfuntion (associated with gamma-IFN). Therefore, the practitioner would turn to trial and error experimentation in order to determine the "conditions" caused by immune system dysfuntion (associated with gamma-IFN) in mammals that would respond to the claimed method of treatment (employing the claimed composition). Therefore, undue experimentation becomes the burden of the practitioner.

Claim Rejections - 35 USC § 103

Claims 26 and 34, 38-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over f Borbe (J. neural. Transm. Suppl. 1990) in view of Barton et al (J. Neurooncol.) and Balsa et al (Biochem. Pharmacol. 1987).

Examiner notes that the office actions dated 10-21-04 and 5-17-05, included claims 26, 34 and 38-62 in the first line of the rejection, whereas the limitations of claims 35-37 have also been addressed in the body of the rejection, along with the limitations of claims 26, 34 and 38-62. Accordingly, the rejection under this section is applicable to claims 26 and 34-62.

Borbe teaches desmethylselegiline (DMS) and selegiline as effective MAO-B inhibitors, which irreversibly blocks MAO-B. Borbe also teaches oral administration of DMS in rats. However, Borbe does not specifically state that DMS is used for treating "a condition produced by immune system dysfunction that is associated with gamma-interferon production", as claimed. Further, Borbe also fails to teach the claimed enantiomer or specific disease conditions.

Barton et al (Barton) analyzed neurological complications in patients suffering from Kaposi's sarcoma and observed that patients suffered neurological dysfuntion that included neoplastic involvement of nervous system, autoimmune disorders or opportunistic infections (abstract). Barton does not suggest any treatment for the above conditions, however, establishes a relation ship between acquired immune deficiency

syndrome, autoimmune disorders, nervous system dysfunction and opportunistic infections.

Balsa et al teaches monoamine oxidase activities in lymphocytes (L) and granulocytes (G), particularly against 5-hydroxytryptamine, benzylamine, beta-phenyl ethylamine etc., as substrates. Balsa et al conclude from their experiments with deprenyl that monoamine oxidase (MAO) activity present in both L and G is predominantly of MAO-B form. Thus, Balsa shows the activity of MAO-B in lymphocytes and granulocytes, the cell types that play a key role in immune system function and Barton teaches that immune deficiency is related to conditions such as cancer, neurological dysfunction, infection and AIDS. Therefore, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use DMS of Borbe for reducing the MAO-B activity in lymphocytes and granulocytes, which in turn play an important role in the development of immune deficient disorders such as Kaposi's' sarcoma, AIDS or other opportunistic infections because Barton associates immune dysfunction with conditions such as AIDS, Kaposi's' sarcoma etc., and Balsa teaches that activity of MAO-B is predominant in G and L cells , which can be effectively inhibited by deprenyl. One of an ordinary skill in the art would have expected DMS, a monoamine oxidase inhibitor, to be effective in treating AIDS, tumors, cancers and other immune deficient conditions by inhibiting the action of MAO-B of immune cells i.e., lymphocytes and granulocytes. While the above references do not explicitly state a reduction in the levels of gamma-IFN, absent showing the evidence to the contrary, it is the position of the examiner that the claimed composition implicitly restores the levels of

gamma-IFN. Furthermore, optimization of claimed dosage of DMS and choosing the appropriate routes of administration, with an expectation to obtain the desired therapeutic effect would have been within the scope of a skilled artisan.

(10) Response to Argument

Appellant's arguments filed have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

Appellants argue that the examiner has not met her burden of establishing a reasonable basis to question the enablement provided for the claimed subject matter. Appellants assert that the claims are enabled because it is well within the skill of one in the art to determine whether a condition produced by immune system dysfunction is associated with reduced levels of gamma-interferon production, and whether administering the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof leads to an increase in gamma-interferon production. It is argued that the underlying complexity of the immune system does not mean that the pending claims are not enabled and that measuring reduced levels or increased levels of gamma-interferon in a mammal are well within the skill of one in the art, and do not require undue experimentation.

Appellants also argue that whether or not the claims will encompass multiple complex diseases or disorders is irrelevant to the question of enablement, since one of

skill in the art will clearly be able to identify conditions produced by immune system dysfunction associated with reduced levels of gamma-interferon production and that one of skill in the art can identify conditions that fall within the genus of conditions produced by immune system dysfunction is associated with reduced levels of gamma-interferon production without undue experimentation, as supported by as Exhibit 1 (attached to the Appeal Brief), which clarifies the correlation of IFN-gamma to conditions related to immune deficiency such as cancer and AIDS, as well as autoimmune diseases due to the central role of IFN-gamma in the immune system. It is argued that the reference states "Adequate function of the IFN-y/macrophage system is essential for natural as well as acquired resistance to infection and cancer. Malfunctioning of the system is recognized to be instrumental in inflammatory and autoimmune disease".

Appellants arguments have been considered but not found persuasive because appellants have not provided nor shown how one of an ordinary skill in the art would readily recognize that a particular condition such as cancer (acute or chronic) or Alzheimer's' or a specific condition in the AIDS syndrome (such as an infection or Kaposi's sarcoma) is always associated with reduced levels of gamma-interferon. Appellants themselves stated that there is an underlying complexity in the immune system function due to the interplay of several interleukins, cytokines, and growth factors. While it is true that reduced gamma-interferon is recognized as one of the causes of some or certain disease or disordered conditions, there is no guidance in the instant specification as to how one of an ordinary skill in the art would recognize that it is

the levels of gamma-interferon alone that caused the conditions or which of the specific conditions in complex diseases such as AIDS or cancer. Further, appellants have neither described nor shown that a reduced gamma-interferon is a definite causative factor for the claimed "immune dysfunction". This is supported by appellants' own statement that the scope of claims is not directed to those conditions that have reduced gamma-interferon production but no immune system dysfunction (page 13, first paragraph of the Appeal Brief). In other words, reduced levels of gamma-interferon do not always cause immune dysfunction. Accordingly, a person in need of a treatment for a disease or disorder can only recognize the symptoms of the particular disease or disorder, but not the underlying causes. Thus, absent any showing or guidance in the instant specification that the conditions and diseases can only be caused by reduced gamma-interferon and not due to any other underlying cause (for instance an increased tumor necrosis factor or altered levels of any other interleukin or cytokine), why one of an ordinary skill in the art would tend to measure the IFN-gamma levels, when the diseases or disorders can also be caused by other cytokines or cytokines etc., and then treat such conditions by administering R(-) desmethylselegiline.

Appellants argument that instant specification provides enough guidance to readily determine the effective amount of R(-) DMS to achieve the therapeutic effect (as described on page 9 of the specification) is not persuasive because the description only provides a general statement of optimizing the dosage depending on the severity of disease or condition. This description together with the statement that an initial dose of 0.015 mg/kg is administered, followed by a progressively higher dosage as required,

only suggests that a practitioner has to turn to trial and error in each patient, in order achieve a therapeutic response.

Appellants argue that examiner improperly inserted the limitation of complete treatment of the claimed conditions. While it is true that the treatment does not necessarily mean a cure for the claimed conditions, examiner still maintains the argument that the breadth of the instant "treatment" extends to conditions that are yet to be identified as being associated or caused by reduced levels of gamma-IFN. Besides, appellants also did not provide any guidance or rationale that a reduced gamma-IFN level is necessarily associated with clinical conditions that require treatment and that restoring the gamma-IFN levels provides a therapeutically effective treatment for all the conditions that are associated with reduced levels of IFN. Thus, the specification enables only restoration of gamma-IFN levels by treating with the claimed DMS enantiomer but does not provide guidance to one of an ordinary skill in the art at the time of the instant invention to treat all the conditions associated with the reduced levels of IFN-gamma and provide a therapy for the same.

With respect to the argument that instant specification sets forth examples of AIDS and age-related immune system function losses as two representative examples of conditions associated with the reduced levels of gamma-IFN, it is examiner's position that both the conditions exemplified are complex conditions, and appellants have not shown that AIDS per se can be treated by improving or increasing the levels of gamma-IFN. Instant specification only supports that administering the claimed compound

increases the levels of gamma-IFN (page 17 of the Brief) but does not show that such an increase definitely treats the claimed conditions.

Claim Rejections - 35 USC § 103

Appellants argue that there is no prima facie case of obviousness established, as there is no motivation or suggestion to combine the reference teachings and no reasonable expectation of success. Appellants argue that the combination of references do not teach or suggest all elements of the pending claims because as the office action also admits the references do not state a reduction in the levels of interferon (a condition that is present in each of the pending claims). Appellants argue that in the absence of any explanation by examiner, why one of skill in the art would expect that inhibiting MAO-B activity in lymphocytes and granulocytes would treat conditions produced by reduced gamma-FN.

Appellants arguments are not persuasive because the claims require a method of treating a condition that is associated with reduced IFN levels and specifically recite AIDS, cancer etc. The claims are not directed to a method of restoring IFN levels and hence condition associated with reduced levels of gamma-IFN is not a positive limitation. Further, the reduced levels of IFN are implicit in the conditions taught by Barton. This is further supported appellants argument regarding the enablement of instant method (see the above sections), where appellants argued that reduced levels of gamma-IFN plays a role in immune system dysfunction and also provided evidence

that conditions such as cancer and AIDS are related to immune deficiency, as evidenced by exhibit A (submitted by appellants in response to enablement rejection of record). In this regard, appellants have not shown that the conditions taught by Barton et al are not associated with reduced levels of gamma-IFN. Instant specification teaches the claimed compounds as MAO inhibitors, which the cited reference of Borbe also teaches. Further, the motivation to use the compounds of Borbe for treating the immune deficiency related conditions (of Barton) comes from the teaching of Balsa that the same enzyme MAO-B is present in the lymphocytes and granulocytes, the cell types that play a key role in the immune system function (or dysfunction) leading to the diseases or conditions of immune system dysfunction. Appellants argue that Barton and Balsa are unrelated to Borbe because they fail to teach the claimed compound. However, instant rejection is based on a combination of the teachings. Barton teaches the conditions associated with immune dysfunction, whereas Balsa establishes MAO-B activity in lymphocytes and granulocytes play a key role in immune system function (or dysfunction) and that deprenyl effectively inhibits the MAO-B activity in these cells. Borbe further states that deprenyl and DMS are equally effective in their MAO-B inhibitory activity. Therfore, one of an ordinary skill in the art would have expected DMS of Borbe to be effective in inhibiting the MAO-B activity of lymphocytes and granulocytes, that play a key role in immune system function, which in turn modulates the immune and provide treatment for the conditions associated with immune dysfunction such as such as Kaposi's sarcoma (Balsa). While the cited references do not teach the levels of gamma-interferon, appellants have not shown that the conditions

described by Barton are not associated with reduced levels of gamma-IFN. Further, appellants admit that the claims are not directed to underlying mechanism of reduced levels of IFN and instead directed to treating the conditions. Accordingly, the combination of references cited provide motivation to employ R(-)DMS of Borbe for treating immune dysfunction conditions such as Kaposi's sarcoma, as explained above, with a reasonable expectation of inhibiting the MAO-B activity in the lymphocytes and granulocytes (which in turn are important for immune function) and thus maintain proper functioning of the immune system.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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